Kidney International, Vol. 64 (2003), pp. 579–584

Chlamydia pneumoniae, overall and cardiovascular mortality in end-stage renal disease (ESRD)

Carmine Zoccali, Francesca Mallamaci, Giovanni Tripepi, Saverio Parlongo,† Sebastiano Cutrupi, Frank Antonio Benedetto, Grazia Bonanno, Giuseppe Seminara, Pasquale Fatuzzo, Francesco Rapisarda, and Lorenzo Salvatore Malatino

National Research Council (CNR), Institute of Biomedicine, Clinical Epidemiology and Physiopathology of Renal Diseases and Hypertension, Reggio Calabria, Italy; Cardiology Unit, Ospedale Morelli, Reggio Calabria, Italy; Institute of Internal Medicine "L. Condorelli," Catania University, Catania, Italy; and Institute of Internal Medicine and Geriatry, Catania University, Catania, Italy

***Chlamydia pneumoniae*, overall and cardiovascular mortality in end-stage renal disease (ESRD).**

Background. Cross-sectional and retrospective studies suggest that *Chlamydia pneumoniae* infection may contribute importantly to the high cardiovascular risk of patients with end-stage renal disease (ESRD).

Methods. We investigated the relationship between *C. pneumoniae* serology and survival and incident fatal cardiovascular events in a cohort of 227 ESRD patients (follow-up of 39 ± 20 months).

Results. On univariate Cox regression analysis patients with anti-*C. pneumoniae* immunogloblulin A (IgA) titer ≥1:16 had a significantly higher risk of all-cause and cardiovascular mortality when compared to patients without IgA antibodies. However, after data adjustment for age and smoking, the hazard ratio (HR) decreased substantially and became largely nonsignificant. Adjustments for traditional and nontraditional risk factors further decreased the independent association of IgA anti-*C. pneumoniae* and these outcomes (all-cause mortality HR, 1.08; 95% CI, 0.68 to 1.72; $P = 0.74$; cardiovascular mortality HR, 1.07; 95% CI, 0.60 to 1.89; $P = 0.83$). A similar loss of prognostic power was observed for IgG anti-*C. pneumoniae* so that in fully adjusted models the HRs were very close to those observed for IgA anti-*C. pneumoniae* (all-cause mortality HR, 1.13; 95% CI, 0.68 to 1.86, $P = 0.64$; cardiovascular mortality HR, 1.10; 95% CI, 0.60 to 2.00; $P = 0.77$).

Conclusion. C. pneumoniae seropositivity is associated to shorter survival and incident fatal cardiovascular events in patients with ESRD but these associations are in large part attributable to the link between *C. pneumoniae* and well-established, traditional risk factors. It is highly unlikely that *C. pneumoniae* infection is a major risk factor in patients with ESRD.

† Deceased.

Key words: cardiovascular risk, chlamydia, dialysis, ESRD, survival, uremia.

Received for publication December 23, 2002
and in revised form February 8, 2003
Accepted for publication March 17, 2003

Cardiovascular mortality in patients with end-stage renal disease (ESRD) is a problem of epidemic dimensions [1, 2]. In recent years inflammation has emerged as a major cardiovascular risk factor in this population [3–6]. However, the cause of inflammation in ESRD is still uncertain and hemodialysis-related, genetic, and infectious causes have been implicated in this process [7]. It has been hypothesized that raised C-reactive protein (CRP) may be an indicator of chronic infections possibly correlated with risk of coronary heart disease, such as bronchopulmonary infection with *Chlamydia pneumoniae*. In line with this possibility it was found that the serum titre of anti-*C. pneumoniae* antibodies is directly related to the severity of carotid atherosclerosis both in patients with chronic renal diseases [8] and in dialysis patients [5, 9]. Furthermore, a retrospective cohort study of small dimensions has recently reported that the presence of anti-*C. pneumoniae* antibodies predicts survival in patients treated by peritoneal dialysis [10].

Long-term prospective studies with data collected on many possible confounders or mediators may help to distinguish whether the link between *C. pneumoniae* and cardiovascular complications is truly independent of other risk factors since this approach is generally less influenced than surveys and retrospective studies by any effect of preexisting disease itself on the factors being investigated. We report the relationship between *C. pneumoniae* seropositivity and all-cause and cardiovascular mortality in the Cardiovascular Risk Extended Evaluation in Dialysis (CREED) study, an ongoing prospective study aimed at investigating risk factors in the ESRD population.

METHODS

Protocol

The protocol was in conformity to the ethical guidelines of our institutions and informed consent was obtained

from each participant. All studies were performed during a nondialysis day, between 8:00 A.M. and 10:00 A.M.

Study cohort

The inception cohort was enrolled between January 1997 and May 1998 and was composed of 227 patients with ESRD (126 males and 101 females) without history of congestive heart failure and without intercurrent illnesses. These patients had been on regular dialysis treatment for at least 6 months (median duration of regular dialysis treatment, 42 months; interquartile range, 21 to 106 months). The prevalence of diabetes mellitus in this cohort was 15% (i.e., 35 patients out of 227).

All patients were virtually anuric (24-hour urine volume <200 mL/day) and were being treated three times a week with standard bicarbonate dialysis (sodium, 138 mmol/L; HCO_3, 35 mmol/L; potassium, 1.5 mmol/L; calcium, 1.25 mmol/L; and magnesium, 0.75 mmol/L) and cuprophan or semisynthetic membranes (dialysis filters surface area, 1.1 to 1.7 m^2). The average urea Kt/V in these patients was 1.21 ± 0.27. Eighty-five patients were habitual smokers (21 ± 16 cigarettes/day). One hundred and twenty-two patients were on treatment with erythropoietin. Eighty-three patients were being treated with antihypertensive drugs [58 on monotherapy with angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 receptors (AT-1) antagonists, calcium channel blockers, and alpha and beta blockers and 25 on double or triple therapy with various combinations of these drugs]. After the initial assessment patients were followed up for an average time of 39 months (range, 0.2 to 62.0 months). During the follow-up, fatal cardiovascular events (myocardial infarction, heart failure, stroke, pulmonary embolism, arrhythmia, sudden death, mesenteric infarction, and peripheral vascular disease) and death were accurately recorded. Each death was reviewed and assigned an underlying cause by a panel of five physicians. As a part of the review process, all available medical information about each death was collected. This information always included study and hospitalization records. In the case of an out-of-hospital death, family members were interviewed by telephone to better ascertain the circumstances surrounding death.

Laboratory measurements

Blood sampling was performed after an overnight fast between 8.00 A.M. and 10.00 A.M. always during a nondialysis day. After 20 to 30 minutes of quiet resting in semirecumbent position, samples were taken into chilled ethylenediaminetetraacetic acid (EDTA) vacutainers, placed immediately on ice, centrifuged within 30 minutes at –4°C, and the plasma stored at –80°C before assay. Serum lipids, albumin, calcium, phosphate, and hemoglobin measurements were made using standard methods in the routine clinical laboratory. CRP and plasma homocysteine were measured as reported elsewhere [5]. Immunoglobulin G and A (IgG) and (IgA)-specific antibodies for *C. pneumoniae* were determined by using a semiquantitative commercially available kit (Labsystems OY, Helsinki, Finland), which is 100% specific and 97% sensitive. This method was based on an indirect solid-phase enzyme immunoassay with horseradish peroxidase as a marker enzyme (intra-assay cardiovascular %, 4% to 6%). IgG and IgA *C. pneumoniae* antibody titers were analyzed as three categories (IgG antibodies, undetectable, at a dilution of 1 in 32 and at a dilution of ≥1 in 64 and IgA antibodies, undetectable, at a dilution of 1 in 8 and at a dilution of ≥1 in 16).

Statistical analysis

Data are reported as mean ± SD, median and interquartile range, or as percent frequency and comparisons between groups were made by one-way analysis of variance (ANOVA), Kruskal-Wallis test, or chi-square test, as appropriate. The relationship between ordinal variables was tested by Spearman rank correlation.

The predictive power of IgG and IgA *C. pneumoniae* titers for all-cause and cardiovascular mortality was analyzed by Cox's proportional hazards models at different levels of data adjustment: IgG or IgA titer only (unadjusted); model 1 = age- and smoking-adjusted; model 2 = model 1 + other Framingham risk factors (gender, diabetes, systolic blood pressure, serum cholesterol, and previous cardiovascular events). Furthermore, we forced into model 2 (Framingham risk factor–based model) risk factors peculiar to ESRD (serum albumin, hemoglobin, and calcium x phosphate) and emerging risk factors (serum CRP and plasma homocysteine). Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated with the use of the estimated regression coefficients and their standard errors in the Cox regression analysis. The assumption of linearity for the Cox models was examined through visual inspection and no violation of proportional hazards was found. There were no missing values for anti-*C. pneumoniae* antibodies. Ten patients had missing values for other covariates. Two were missing cholesterol levels; one did not have hemoglobin level; two did not have albumin measures; three were missing calcium and phosphate; and two did not have CRP values. Missing values for these covariates were set to the mean value. All calculations were done using a standard statistical package (SPSS for Windows, version 9.0.1, Chicago, IL, USA).

RESULTS

Eighty-nine patients (39%) were positive for IgA anti-*C. pneumoniae* antibodies (1:8 in 24 cases and ≥1:16 in the remaining 65 cases). One hundred and seventeen patients (51%) were positive for IgG anti-*C. pneumoniae*

Table 1. Somatometric, clinical, and biochemical data of patients divided on the basis of immunoglobulin A (IgA) anti-chlamydia titers

	IgA anti-chlamydia titers			
	Seronegative ($N = 138$)	1:8 ($N = 24$)	≥1:16 ($N = 65$)	*P* value
Age *years*	57.1 ± 15.0	59.5 ± 14.7	66.5 ± 13.0	<0.001
Males *number* (%)	69 (50%)	16 (67%)	41 (63%)	0.11
Diabetes *number* (%)	14 (10%)	6 (25%)	15 (23%)	0.02
Smokers *number* (%)	42 (30%)	12 (50%)	31 (48%)	0.02
Systolic blood pressure *mm Hg*	139.7 ± 24.6	131.4 ± 26.6	142.8 ± 25.1	0.16
Diastolic blood pressure *mm Hg*	76.6 ± 12.1	72.7 ± 12.6	75.8 ± 14.2	0.37
Cholesterol *mmol/L*	5.58 ± 1.62	5.14 ± 1.25	5.01 ± 1.20	0.03
Hemoglobin *g/L*	108.1 ± 18.6	108.8 ± 19.2	106.1 ± 18.7	0.73
Albumin *g/L*	42.1 ± 5.1	41.8 ± 4.1	40.3 ± 4.3	0.04
Calcium *mmol/L*	2.31 ± 0.27	2.20 ± 0.26	2.22 ± 0.20	0.04
Phosphate *mmol/L*	1.98 ± 0.42	2.06 ± 0.53	1.95 ± 0.47	0.58
Patients with previous cardiovascular events *number* (%)	55 (40%)	9 (37%)	31 (48%)	0.52
Homocysteine *μmol/L*	26.7 (19.4–46.8)	26.9 (19.5–41.2)	27.5 (19.6–35.3)	0.70
C-reactive protein *mg/L*	7.8 (3.4–16.3)	4.5 (3.4–11.6)	8.2 (3.4–19.1)	0.24

Data are reported as mean ± SD, median and interquartile range or as percent frequency, as appropriate.

antibodies (1:32 in 53 cases and ≥1:64 in the remaining 64 cases). On univariate analysis IgG and IgA *C. pneumoniae* antibodies were strongly interrelated (Spearman rank, $r = 0.65$, $P < 0.001$). Patients with high titer of IgA anti-*C. pneumoniae* antibodies (Table 1) were older, more likely to be diabetics and smokers, and were characterized by a lower serum total cholesterol, albumin, and calcium and a higher proportion of males when compared to remaining patients. When the study cohort was reclassified on the basis of IgG anti-*C. pneumoniae* antibodies patients with a high titer differed from those with a low or normal titer for all but serum albumin and calcium the above-mentioned risk factors.

IgG and IgA anti-*C. pneumoniae* titers, all-cause, and cardiovascular mortality

During the 39 ± 20 months of the follow-up period, 102 patients died, 69 of them (i.e., 68% of total deaths) of cardiovascular causes (Table 2).

Table 2. Causes of death in the study cohort

	Number
Cardiovascular	
Stroke	19
Myocardial infarction	16
Heart failure	14
Sudden death	7
Mesenteric infarction	5
Arrhythmia	4
Pulmonary embolism	3
Severe peripheral vascular disease	1
Total	69
Other causes	
Sepsis/infection	10
Cachexia	7
Neoplasia	5
Hyperkalemia	4
Gastrointestinal hemorrhage	3
Diabetes, hyperosmolar coma	1
Treatment withdrawal	1
Chronic obstructive pulmonary disease	1
Hemoptysis	1
Total	33

On univariate Cox regression analysis patients with anti-*C. pneumoniae* IgA titer ≥1:16 had a significantly higher risk of all-cause and cardiovascular mortality when compared to patients without IgA antibodies (Tables 3 and 4 unadjusted model). However, after data adjustment for age and smoking, the HR of IgA anti-*C. pneumoniae* titers for all-cause and cardiovascular mortality decreased substantially and became largely nonsignificant (Tables 3 and 4, Model 1). Adjustments for other traditional risk factors (gender, diabetes, cholesterol, hypertension, and previous cardiovascular events) (Tables 3 and 4, Model 2) further decreased the independent association of IgA anti-*C. pneumoniae* and these outcomes. Forcing factors peculiar to ESRD (anemia, calcium x phosphate product and albumin) and emerging risk factors (CRP and homocysteine) into model 2 did not modify the HR of IgA anti-*C. pneumoniae* (all-cause mortality HR, 1.08; 95% CI, 0.68 to 1.72; $P = 0.74$; cardiovascular mortality HR, 1.07; 95% CI, 0.60 to 1.89; $P = 0.83$).

A similar loss of prognostic power was observed for IgG anti-*C. pneumoniae* so that in statistical models adjusted for age and smoking the contribution of IgG anti-*C. pneumoniae* titer to explain the incidence of these outcomes was low and not significant (all-cause mortality HR, 1.24; 95% CI, 0.78 to 2.00; $P = 0.36$; cardiovascular mortality HR, 1.23; 95% CI, 0.70 to 2.16; $P = 0.47$). Further adjustment for traditional risk factors produced HRs very close to those observed for IgA anti-*C. pneumoniae* (all-cause mortality HR, 1.13; 95% CI, 0.68 to 1.86; $P = 0.64$; cardiovascular mortality HR, 1.10; 95% CI, 0.60 to 2.00; $P = 0.77$).

Table 3. Cox regression analysis: Immunoglobulin A (IgA) anti-chlamydia based model (all-cause death)

Variables (units of increase)	Unadjusted	Model 1 (Age and smoking adjusted)	Model 2 (Adjusted for Framingham risk factors)
IgA anti-chlamydia titer			
0 = seronegative	1[a]	1[a]	1[a]
1 = IgA titre 1:8	1.22 (0.64–2.34), $P = 0.55$	1.03 (0.54–2.00), $P = 0.92$	0.99 (0.50–1.95), $P = 0.97$
2 = IgA titre ≥1:16	1.89 (1.25–2.87), $P = 0.003$	1.21 (0.79–1.87), $P = 0.39$	1.09 (0.69–1.71), $P = 0.72$
Age (1 year)		1.05 (1.03–1.07), $P < 0.001$	1.05 (1.03–1.07), $P < 0.001$
Smoking		1.90 (1.27–2.85), $P = 0.002$	1.43 (0.88–2.34), $P = 0.15$
Male gender			1.78 (1.06–3.00), $P = 0.03$
Diabetes			1.83 (1.14–2.95), $P = 0.01$
Cholesterol (1 mmol/L)			1.06 (0.92–1.22), $P = 0.43$
Systolic blood pressure (1 mm Hg)			1.00 (0.99–1.01), $P = 0.89$
Previous cardiovascular events			2.25 (1.47–3.44), $P < 0.001$

Data are expressed as hazard ratios, 95% CI, and *P* values.
[a]Reference group

Table 4. Cox regression analysis: Immunoglobulin A (IgA) anti-chlamydia based model (cardiovascular mortality)

Variables (units of increase)	Unadjusted	Model 1 (Age and smoking adjusted)	Model 2 (Adjusted for Framingham risk factors)
IgA anti-chlamydia titre			
0 = seronegative	1[a]	1[a]	1[a]
1 = IgA titre 1:8	1.65 (0.82–3.34), $P = 0.16$	1.40 (0.69–2.85), $P = 0.36$	1.40 (0.67–2.94), $P = 0.37$
2 = IgA titre ≥1:16	1.77 (1.05–2.98), $P = 0.03$	1.16 (0.68–1.98), $P = 0.58$	1.00 (0.57–1.77), $P = 0.99$
Age (1 year)		1.05 (1.03–1.08), $P < 0.001$	1.05 (1.03–1.08), $P < 0.001$
Smoking		2.24 (1.38–3.65), $P = 0.001$	1.70 (0.94–3.05), $P = 0.08$
Male gender			1.92 (1.00–3.67), $P = 0.05$
Diabetes			1.77 (0.98–3.19), $P = 0.06$
Cholesterol (1 mmol/L)			1.11 (0.94–1.32), $P = 0.21$
Systolic blood pressure (1 mm Hg)			1.00 (0.99–1.01), $P = 0.46$
Previous cardiovascular events			2.35 (1.39–3.98), $P = 0.001$

Data are expressed as hazard ratios, 95% CI, and *P* values.
[a]Reference group

Combined analysis of IgA and IgG anti-*C. pneumoniae* antibodies (anti-IgA ≥1:16 and/or anti-IgG ≥1:64) failed to materially increase the prediction power of chlamydia serology for all-cause (HR, 1.11; 95% CI, 0.68 to 1.83; $P = 0.68$) and cardiovascular death (HR, 1.00; 95% CI, 0.55 to 1.84; $P = 0.99$) in Cox models, including all Framingham risk factors.

DISCUSSION

This study shows that in ESRD high IgA and IgG anti-*C. pneumoniae* titers are associated with shorter survival and incident cardiovascular complications only on crude analysis and that after simple adjustment for age and smoking and other traditional risk factors the relative risk of chlamydia seropositivity for all-cause and cardiovascular mortality is of slight degree and largely nonsignificant.

Cardiovascular risk factors in ESRD

Patients with ESRD have a high burden of traditional (Framingham) risk factors. Indeed diabetes, hypertension, smoking, and alterations in the lipid profile are highly prevalent in ESRD patients. In addition, risk factors peculiar to ESRD, like anemia [11] and high phosphate and calcium x phosphate product [12], as well as emerging risk factors, like hyperhomocysteinemia [13, 14] and microinflammatory processes [3–6], play an important role in the high cardiovascular risk of these patients. The causes of microinflammation and elevated CRP in ESRD are largely unknown and because uremic patients have compromised immune defense [15], it is suspected that inflammation may be in part due to low-grade, subclinical chronic infections [7].

Anti-chlamydia antibodies and cardiovascular risk in ESRD

C. pneumoniae has been linked to atherosclerosis and coronary heart disease in the general population but it remains unclear whether this association entails a causal link [16]. In 1999, we suggested that subclinical chlamydial infection may be implicated in atherosclerosis in ESRD in that we found that IgG anti-*C. pneumoniae* titer was related to serum CRP as well as to number of atherosclerotic plaques [9] in the carotid arteries in patients on chronic dialysis. In a subsequent study Sten-

vinkel et al [4] reported an association between a high IgA anti-*C. pneumoniae* titer with increased intima media cross-sectional area in patients with chronic renal insufficiency maintained on conservative treatment. A high IgA anti-*C. pneumoniae* titer has also been associated with larger carotid plaques [17] and progression in intimal lesions in dialysis patients [18] and with the angiographic presence of coronary heart disease in patients with chronic renal failure [19]. Very recently chlamydia IgG seropositivity has been related to coronary calcium score and to increased intima media thickness in a group of 39 patients with childhood-onset ESRD [20]. In line with the hypothesis that chlamydia infection may be an important risk factor for atherosclerotic complications in ESRD, an association was found between a high IgA anti-*C. pneumoniae* titer and cardiovascular events in a small study in continuous ambulatory peritoneal dialysis (CAPD) patients [10]. Of note in these studies the relative risk for atherosclerosis or atherosclerotic complications was high and ranged from 1.7 [19] to 7.2 [10] The relationship between chlamydia serology and cardiovascular outcomes has never been examined in a prospective cohort study in patients with ESRD. In comparison with surveys and retrospective studies, prospective studies reduce selection biases, minimize any influence of disease itself on the factor being investigated, and may include better adjustment for potential confounding factors. In this regard, it is important to note that statistical adjustment for established risk factors was incomplete in most studies in ESRD [17–19].

The presence of elevated IgA anti-*C. pneumoniae* titer has been shown to reflect chronic chlamydia infection [21], while it is unclear whether increased levels of IgG antibodies reflect the duration of infection or reactivation of a latent infection. Accordingly, most of the previously reported studies in ESRD describing an association between chlamydia and atherosclerotic complications quantified the severity of infection by measuring IgA antibodies. In this prospective study, we found univariate associations between survival and incident fatal cardiovascular events with both IgA and IgG anti-*C. pneumoniae* titers and IgA antibodies tended to be more strongly related to these outcomes. However, after adjustment for age and smoking, both IgA and IgG anti-*C. pneumoniae* titers were no longer significant, suggesting that the link between all-cause and cardiovascular mortality and chlamydia serology is confounded by these risk factors. Statistical adjustment in observational studies should be carefully performed because a true causal link may be obscured by adjustment for covariate(s), which are in the pathogenetic chain of events triggered by the factor being evaluated [22]. However we found that *C. pneumoniae* antibodies lost most of their prediction power after simple adjustment for age and smoking, which are recognized confounding factors in the general population [23]. Furthermore, models adjusted for traditional risk factors or fully adjusted models were compatible with a slight association or no association at all (no risk excess).

Overall, our results in patients with ESRD are similar to observations by Danesh et al [23] and to a large prospective study in 21,520 professional men aged 35 to 64 years who attended a private medical organization in London [24]. Our study had a 80% power to detect a HR equal to or greater than 1.50 with a P value <0.05. Thus, we can reliably exclude any strong association between *C. pneumoniae* IgA and IgG titers and all cause and cardiovascular mortality in patients with ESRD.

Study limitations

We did not measure repeatedly anti-chlamydia antibodies during the follow-up and therefore we could not correct for possible underestimation due to fluctuations in serum antibody titers within individuals over time (regression dilution bias). Larger studies are still required to show associations of moderate or a slight degree in patients with ESRD. Furthermore, our study cohort was composed of middle age and old individuals. Therefore our data cannot be extrapolated at younger ages when associations between infectious agents and cardiovascular complications seem to be stronger [25].

CONCLUSION

Chlamydia seropositivity is associated to shorter survival and incident fatal cardiovascular events in patients with ESRD but these associations are in large part attributable to the link between chlamydia and well-established, traditional risk factors. It is highly unlikely that chlamydia infection is a major risk factor in patients with ESRD.

Reprint requests to Professor Carmine Zoccali, CNR, Istituto di Biomedicina, Epidemiologia Clinica e Fisiopatologia, delle Malattie Renali e dell'Ipertensione Arteriosa, c/o Ospedali Riuniti, Via Vallone Petrara, 89124 Reggio, Calabria, Italy.
E-mail: carmine.zoccali@tin.it

REFERENCES

1. Levey AS: Controlling the epidemic of cardiovascular disease in chronic renal disease: Where do we start? *Am J Kidney Dis* 32(Suppl 3):S5–S13, 1998
2. Baigent C, Burbury K, Wheeler D: Premature cardiovascular disease in chronic renal failure. *Lancet* 356:147–152, 2000
3. Zimmermann J, Herrlinger S, Pruy A, *et al*: Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 55:648–658, 1999
4. Stenvinkel P, Heimburger O, Paultre F, *et al*: Strong association between malnutrition, inflammation and atherosclerosis in chronic renal failure. *Kidney Int* 55:1899–1911, 1999
5. Zoccali C, Benedetto FA, Mallamaci F, *et al*: Inflammation is associated with carotid atherosclerosis in dialysis patients. *J Hypertens* 18:1207–1213, 2000
6. Yeun JY, Levine RA, Mantadilok V, Kaysen GA: C-reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 35:469–476, 2000

7. Kaysen GA: The microinflammatory state in uremia: causes and potential consequences. *J Am Soc Nephrol* 12:1549–1557, 2001
8. Stenvinkel P, Heimburger O, Jogestrand T, *et al*: Does persistent infection with *Chlamydia pneumoniae* increase the risk of atherosclerosis in chronic renal failure? *Kidney Int* 55:2531–2532, 1999
9. Zoccali C and the Creed Investigators: C-reactive protein and atherosclerosis in dialysis patients. *Nephrol Dial Transplant* 13: 2710–2711, 1998
10. Haubitz M, Brunkhorst R: C-reactive protein and chronic *Chlamydia pneumoniae* infection-long-term predictors for cardiovascular disease and survival in patients on peritoneal dialysis. *Nephrol Dial Transplant* 16:809–815, 2001
11. Foley RN, Parfrey PS, Harnett JD, *et al*: The impact of anemia on cardiomyopathy, morbidity, and and mortality in end-stage renal disease. *Am J Kidney Dis* 28:53–61, 1996
12. Block GA, Hulbert-Shearon TE, Levin NW, Port FK: Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 31:607–617, 1998
13. Moustapha A, Naso A, Nahlawi M, *et al*: Prospective study of hyperhomocysteinemia as an adverse cardiovascular risk factor in end-stage renal disease. *Circulation* 97:138–141, 1998
14. Mallamaci F, Zoccali C, Tripepi G, *et al*: The CREED Investigators: Hyperhomocysteinemia predicts cardiovascular outcomes in hemodialysis patients. *Kidney Int* 61:609–614, 2002
15. Kimmel PL, Phillips TM, Simmens SJ, *et al*: Immunologic function and survival in hemodialysis patients. *Kidney Int* 54:236–244, 1998
16. Danesh J, Collins R, Peto R: Chronic infections and coronary heart disease: Is there a link? *Lancet* 350:430–436, 1997
17. Kato A, Odamaki M, Takita T, *et al*: Association between interleukin-6 and carotid atherosclerosis in hemodialysis patients. *Kidney Int* 61:1143–1152, 2002
18. Stenvinkel P, Heimburger O, Jogestrand T: Elevated interleukin-6 predicts progressive carotid artery atherosclerosis in dialysis patients: Association with *Chlamydia pneumoniae* seropositivity. *Am J Kidney Dis* 39:274–282, 2002
19. Song H, Tasaki H, Yashiro A, *et al*: *Chlamydia pneumoniae* infection and accelerated development of coronary artery disease in patients with chronic renal failure. *Clin Nephrol* 56:346–352, 2001
20. Oh J, Wunsch R, Turzer M, *et al*: Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. *Circulation* 106:100–105, 2002
21. Saikku P, Leinonen M, Tenkanen L, *et al*: Chronic *Chlamydia pneumoniae* infection as a risk factor for coronary heart disease in the Helsinki Heart Study. *Ann Intern Med* 116:273–278, 1992
22. West R: Commentary: Adjustment for potential confounders may have been taken too far. *Br Med J* 321:213, 2000
23. Danesh J, Whincup P, Walker M, *et al*: *Chlamydia pneumoniae* IgG titres and coronary heart disease: Prospective study and meta-analysis. *Br Med J* 321:208–213, 2000
24. Wald NJ, Law MR, Morris JK, *et al*: *Chlamydia pneumoniae* infection and mortality from ischaemic heart disease: Large prospective study. *Br Med J* 321:204–207, 2000
25. Danesh J, Youngman L, Clark S, *et al*: *Helicobacter pylori* infection and early onset myocardial infarction: Case-control and sibling pairs study. *Br Med J* 319:1157–1162, 1999